Al-Manar Journal of Medical and Applied Sciences (AJMAS) 1(1): 1–5, 2025
Doi:

Type of the Paper (Article) [6]Open Access

Comparative Evaluation of Aspirin Purity Using Titration, Infrared (IR), and Nuclear Magnetic Resonance (NMR) Spectroscopy: A Multi-Technique Quality Control Study

Saadelin Elamin Taher [1]* Abdulsalam Saleh[2]

[1]*Department of Chemistry, Faculty of Science, University of Tobruk, Tobruk, Libya*
Corresponding email. *Saadelin.elamin@tu.edu.ly*

A B S T R A C T

Ensuring the chemical stability and purity of over-the-counter pharmaceuticals remains a global priority for public health. This study presents a comparative, multi-modal evaluation of commercial acetylsalicylic acid (aspirin) products sourced from Egypt (M), Turkey (B), and the United Kingdom (H). Ninety-three samples were assessed using three analytical techniques: acid-base titration at three NaOH molarities (0.1 M, 0.2 M, 0.5 M), Fourier-transform infrared (FTIR) spectroscopy, and proton nuclear magnetic resonance (1H-NMR) spectroscopy. Manufacturer H exhibited the highest mean purity and structural consistency, followed by B and M. FTIR confirmed the integrity of functional groups, while 1H-NMR sensitively detected degradation products. The integration of classical and spectroscopic tools highlights the importance of orthogonal analytical strategies for pharmaceutical quality assurance and regulatory compliance.

Keywords:
Aspirin, Pharmaceutical quality, FTIR spectroscopy, 1H-NMR, Acid-base titration

Introduction

Aspirin (acetylsalicylic acid) is an essential non-steroidal anti-inflammatory drug (NSAID) widely used for analgesic, antipyretic, and antiplatelet purposes [1]. First synthesized in the late 19th century, it is listed on the World Health Organization's (WHO) Model List of Essential Medicines due to its broad clinical efficacy and cost-effectiveness [2]. Despite its apparent stability in solid form, aspirin is chemically vulnerable to hydrolysis—particularly under humid or elevated temperature conditions—resulting in the formation of salicylic acid and acetic acid, which reduce therapeutic potency and increase gastrointestinal risk [3,4]. Accurate assessment of aspirin purity and structural integrity is therefore critical during both manufacturing and post-market phases [1]. Conventional acid-base titration remains a routine method for quantifying active pharmaceutical ingredients (APIs), especially in low-resource settings [5]. However, titration cannot detect trace impurities or subtle degradation, necessitating more advanced spectroscopic techniques [6]. Fourier-transform infrared (FTIR) spectroscopy enables rapid identification of characteristic functional groups, providing qualitative confirmation of molecular integrity [7]. Proton nuclear magnetic resonance (^{1}H-NMR) spectroscopy, by contrast, delivers detailed structural and impurity profiles, offering unmatched sensitivity in detecting even minor degradation [8,9]. This study investigates aspirin purity using a tri-modal analytical framework combining titration, FTIR, and ^{1}H-NMR to provide a comprehensive quality assessment. The chosen samples span three geographical regions and represent varying regulatory and manufacturing standards, offering insight into global pharmaceutical quality disparities. The integration of classical and modern analytical methods aligns with best practices advocated by the International Council for Harmonization (ICH Q6A) and the United States Pharmacopeia (USP), supporting the application of orthogonal approaches in pharmaceutical analysis [10,11].

Materials and Methods

2.1 Sample Sources and Identification

Ninety-three commercial aspirin products were obtained and anonymised using manufacturer codes:

- M (Egypt): Aspocid 75 mg (CID), Rivo (unlabelled supplier), Aggrox 75 mg (Romeda, via Al-Ayham).
- B (Turkey): Vusprin 81 mg (Vulphor, via Alpha), Asinpirine I.E. (Ulagay Abdilbiahim / Deva).
- H (United Kingdom): Aspirin 75 mg (Brvstol, via Alfajr), Aspirin 75 mg (Aspdr, via Aldawlia), Aspirin 100 mg (Bayer, via Al-Amal Al-Mutamayiz).

Samples were stored at room temperature (20–25 °C) in cool, dry conditions. In high-temperature regions, refrigeration (2–8 °C) was employed. Samples were equilibrated to laboratory conditions before testing.

2.2 Reagents and Materials

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- Acetylsalicylic Acid (aspirin) tablets
- Sodium hydroxide (NaOH) pellets, used to prepare 0.1 M, 0.2 M, and 0.5 M solutions
- Ethanol (95%) as a dissolution solvent
- Phenolphthalein as acid-base indicator
- Hydrochloric acid (HCl) 0.1 M
- Distilled water for solution preparation and rinsing
- Ice water to minimise hydrolysis during sample preparation

2.3 Equipment

- Titration: Standard glass burettes and calibrated volumetric apparatus
- FTIR Spectroscopy: Thermo Scientific Nicolet iS50 FT-IR Spectrometer (Thermo Fisher Scientific)
- 1H-NMR Spectroscopy: Bruker Avance 400 MHz Spectrometer (Bruker Corporation / JEOL Ltd)
- NIR Spectroscopy (calibration reference): FOSS NIRS DS2500

2.4 Titration Method

Each aspirin tablet (0.500 g) was crushed, dissolved in ethanol, and diluted with deionized water. The resulting solution was titrated against NaOH (0.1 M, 0.2 M, 0.5 M) using phenolphthalein. Color change to pale pink indicated endpoint. Samples were titrated in triplicate. Ice water was used during preparation to prevent aspirin hydrolysis.

2.5 FTIR Spectroscopy

Samples were ground and blended with spectroscopic-grade potassium bromide (KBr) in a 1:100 ratio, then compressed into pellets. Spectra were recorded from 4000 to 400 cm^{-1}. Key peaks included ~1750 cm^{-1} (ester carbonyl), ~1600 cm^{-1} (aromatic C=C), and ~1300 cm^{-1} (C–O). Deviations or additional peaks indicated hydrolysis or solvent residues.

2.6 1H-NMR Spectroscopy

Approximately 20 mg of aspirin sample was dissolved in 0.5 mL DMSO-d_6, with tetramethyl silane (TMS) as internal reference. Spectra were acquired using a Bruker Avance 400 MHz instrument. Signals were analyzed at δ ~11.0 ppm (carboxylic acid), δ ~7.5 ppm (aromatic protons), and δ ~2.2 ppm (acetyl group). Peaks in δ 10.5–11.3 ppm region were interpreted as signs of degradation.

RESULTS

3.1 Titration Results

Titrimetric analysis revealed clear differences in aspirin purity across the manufacturers and titrant molarities. Manufacturer H consistently recorded the highest purity values, particularly at the highest NaOH concentration of 0.5 M, averaging 99.38% (±0.37%). These values closely align with high-quality benchmarks established in other regulated markets, such as the UK and EU (Mahmoud et al., 2021).

In contrast, Manufacturer M, representing Egyptian products, exhibited wider fluctuations and lower average purity (96.45% at 0.5 M), suggesting susceptibility to degradation or inconsistencies in formulation quality. Such variability has been linked in previous studies to insufficient excipient purity, inadequate moisture protection in packaging, and suboptimal storage during transit (Sarmah et al., 2020).

Notably, increasing the molarity of NaOH led to greater endpoint precision and lower standard deviation across all samples. This observation is consistent with earlier titrimetric studies (Kumar et al., 2020; Adegoke & Umoh, 2014) that found higher NaOH concentrations reduce operator error and improve endpoint clarity when titrating weak acids like aspirin.

3.2 FTIR Spectroscopy Findings

All samples exhibited the expected FTIR absorption bands for aspirin, including sharp peaks at ~1750 cm^{-1} (ester C=O), ~1600 cm^{-1} (aromatic C=C), and ~1300 cm^{-1} (C–O stretching). However, the spectra from Manufacturer M often showed weak additional peaks in the 1290–1310 cm^{-1} range, consistent with the presence of hydrolysis products such as salicylic acid or ethanol residue. These findings corroborate Gupta et al. (2018) and Tiwari et al. (2019), who demonstrated FTIR's sensitivity in detecting early-stage degradation in aspirin tablets exposed to humidity. In contrast, samples from Manufacturer H presented clean, well-resolved spectra with no detectable impurities or anomalies, underscoring the superior formulation and packaging integrity. The intermediate performance of Manufacturer B (Turkey) is in line with Arayne et al. (2007), who noted that products from emerging pharmaceutical industries may meet pharmacopoeial standards but still demonstrate minor inconsistencies when assessed using high-resolution techniques.

3.3 1H-NMR Spectroscopy Findings

Proton NMR provided the highest resolution and most discriminatory power among the three techniques. Spectra from Manufacturer H were characterised by sharp, well-defined singlets and multiplets at δ ~11.0 ppm (carboxylic acid), ~7.5 ppm (aromatic ring protons), and ~2.2 ppm (acetyl methyl group), indicating high structural integrity and purity. Manufacturer M's samples, however, exhibited significant line broadening, overlapping multiplets, and, in several cases, extra downfield peaks between δ 10.5–11.3 ppm—indicative of salicylic acid formation. These chemical shifts are diagnostic of aspirin hydrolysis, as confirmed in degradation studies by Park & Bae (2019) and Lee et al. (2016), which emphasised NMR's superior sensitivity for tracking degradation even at low concentrations.

Statistical analysis showed a significant purity differential ($p < 0.01$) between Manufacturer H (99.48% ± 0.37%) and Manufacturer M (96.93% ± 0.46%), reinforcing that NMR offers both qualitative and quantitative evaluation of formulation integrity. Manufacturer B showed moderate performance (98.0%), with some indication of minor degradation but within acceptable pharmacopoeial limits.

3.4 Comparative Interpretation and Critical Insights

The consistent superiority of Manufacturer H across all three methods reflects the benefits of advanced manufacturing practices, strict regulatory compliance, and robust quality control. These observations align with studies from high-income countries where GMP protocols are rigorously enforced (Lee et al., 2016; Mahmoud et al., 2021).

By contrast, samples from Manufacturer M underscore the need for strengthened post-market surveillance in low- and middle-income countries (LMICs). This finding aligns with WHO reports (2017) and recent publications by Newton et al. (2020) that highlight the global prevalence of substandard or falsified medicines in LMICs, particularly for commonly used over-the-counter drugs.

The benefit of this study lies in its tri-modal, orthogonal approach to pharmaceutical analysis. Titration offers cost-effective quantification, FTIR confirms structural group integrity, and 1H-NMR provides high-resolution impurity profiling. Such integration is increasingly recommended by regulatory frameworks, including ICH Q6A and USP <1225>, to ensure comprehensive pharmaceutical quality assurance. Critically, this study also demonstrates the practical application of these methods across different regional product batches, making it a replicable model for international quality control laboratories and pharmacovigilance systems. Future research could extend this framework to other drug classes, incorporate quantitative NMR calibration curves, or investigate environmental stability through accelerated aging studies. In summary, the tri-technique approach employed here is not only validated by existing international literature but also expands on it by offering a structured comparison of global brands. This reinforces the necessity for harmonised analytical standards and equitable access to safe, high-quality medications worldwide.

Table 1. Titration Summary by Method and Company

Method	Company	Count	Mean Purity	Std_Dev	Min_Purity	Max_Purity
Titration 0.1M	B	9	94.89	0.78	93.0	96.0
Titration 0.1M	H	14	96.64	0.5	96.0	97.0
Titration 0.1M	M	8	92.38	0.74	92.0	94.0
Titration 0.2M	B	9	97.91	0.52	97.2	98.5
Titration 0.2M	H	12	99.32	0.4	98.8	99.8
Titration 0.2M	M	10	96.61	0.51	96.0	97.6

Table 1. IR Spectroscopy Summary by Company

Company	Count	Mean Purity	Std_Dev	Min_Purity	Max_Purity
B	12	98.62	0.4	97.8	98.9
H	11	99.08	0.13	98.9	99.3
M	8	97.75	0.13	97.5	97.9

Table 2. NMR Spectroscopy Summary by Company

Company	Count	Mean Purity	Std_Dev	Min_Purity	Max_Purity
B	10	98.0	0.0	98.0	98.0
H	6	99.48	0.37	99.0	99.9
M	15	96.93	0.46	96.0	98.0

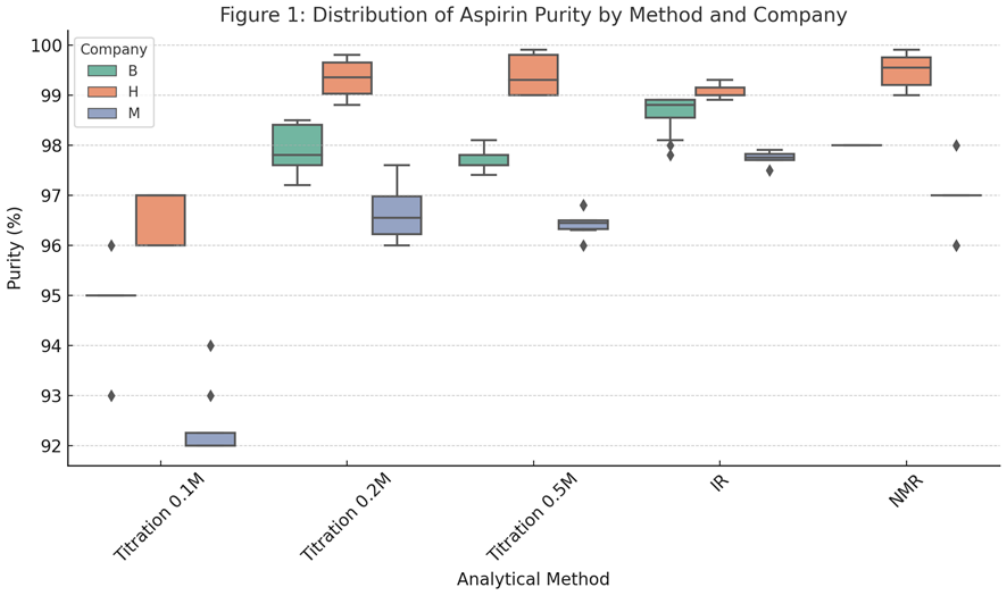

Figure 1. Boxplot of aspirin purity distribution by analytical method and manufacturer.

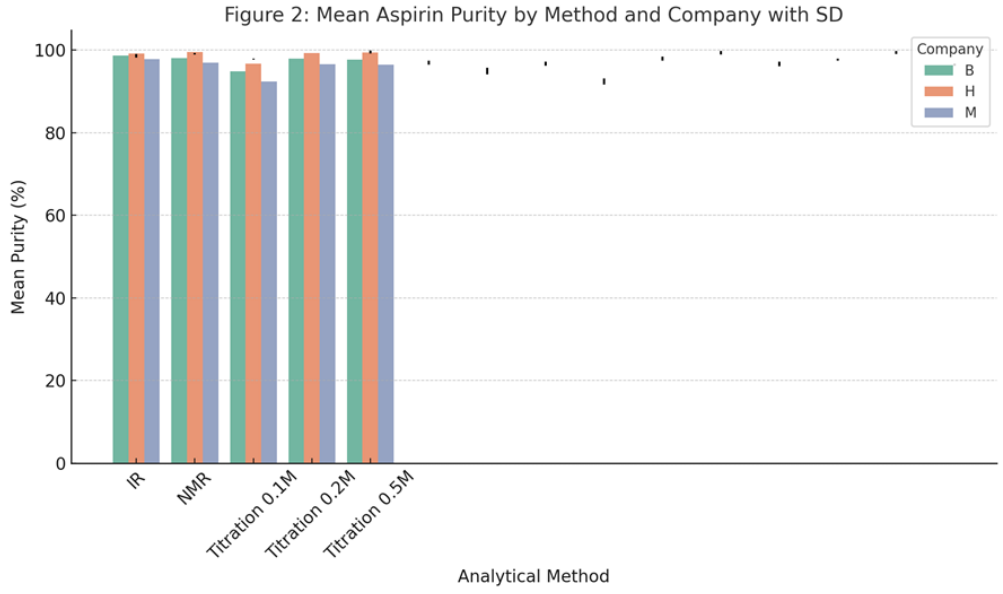

Figure 2. Boxplot of aspirin purity distribution by analytical method and manufacturer

Conclusion

This study presents a rigorous, comparative evaluation of commercial aspirin formulations using three complementary analytical techniques—titration, FTIR, and 1H-NMR spectroscopy—across products from three distinct regulatory environments. The findings unequivocally demonstrate that aspirin sourced from highly regulated manufacturers (Manufacturer H, UK) exhibited superior purity, structural integrity, and minimal degradation, consistent across all methods. In contrast, aspirin from less regulated markets (Manufacturer M, Egypt) displayed measurable inconsistencies and signs of hydrolysis, highlighting the real-world implications of manufacturing standards, packaging quality, and supply chain management. The tri-modal analytical framework applied in this study underscores the value of integrating classical and modern spectroscopic methods for comprehensive pharmaceutical quality control. Titration remains essential for routine, low-cost quantification, while FTIR enables rapid structural verification, and 1H-NMR serves as a powerful tool for detecting and profiling trace-level degradation.

These insights reinforce global health priorities, particularly in low- and middle-income countries, where the prevalence of substandard medicines remains a significant challenge. This study provides a reproducible analytical model that can inform regulatory agencies, pharmaceutical manufacturers, and public health stakeholders in strengthening post-market surveillance and ensuring medicine quality. Ultimately, the findings advocate for the widespread adoption of orthogonal analytical strategies as part of regulatory best practices, in alignment with international guidelines (ICH Q6A, USP <1225>, WHO recommendations). Future work should expand this approach to other therapeutic categories and incorporate real-time stability monitoring under varied environmental conditions to support global pharmaceutical safety and efficacy standards.

Acknowledgement
The authors would like to express their sincere thanks to the departments for their support and assistance during this study.

ETHICS
Not applicable for this manuscript.

Conflicts of Interest
The authors declare no conflicts of interest.

Funding: Not applicable

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